

GAO

Report to the Ranking Minority Member,
Committee on Commerce, House of
Representatives

December 1997

HUMAN TISSUE BANKS

FDA Taking Steps to Improve Safety, but Some Concerns Remain





**United States
General Accounting Office
Washington, D.C. 20548**

**Health, Education, and
Human Services Division**

B-275822

December 5, 1997

The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce
House of Representatives

Dear Mr. Dingell:

Each year human tissue transplants allow approximately 600,000 Americans to live fuller and healthier lives. These transplants aid burn victims, the visually impaired, and persons living with cancer, heart defects, and various other illnesses and injuries. Additionally, transplanting reproductive tissue allows infertile couples to bear children.

Notwithstanding the benefits of tissue transplantation, some are concerned about the potential transmission of infectious diseases from donor to recipient and about certain tissue-processing techniques that may affect the usefulness of tissues or leave them with harmful residues. Because of these concerns, you asked us to evaluate the Food and Drug Administration's (FDA) oversight of transplanted human tissue as well as to evaluate potential safety problems. Specifically, we sought to identify gaps in the current regulation, determining whether and how FDA plans to address them in the approach it has proposed for regulating tissue banking. In this report, we provide our findings and recommendations on these topics for musculoskeletal tissue, skin, corneas, reproductive tissue, and peripheral and umbilical cord blood stem cells.¹

Our examination of the tissue industry was limited to human tissues that are under FDA oversight. We did not examine transfusable blood products or other more specialized FDA-regulated tissue-related products, such as tissues derived from animals, products used to propagate cells or tissues, or products that are extracted from cells or tissues. We also did not examine FDA's regulation of highly manipulated cellular techniques, such as those used in somatic cell therapies.

¹We do not discuss solid organs such as hearts, livers, kidneys, pancreatic tissue, and lungs or bone marrow. The National Organ Transplant Act of 1984 provides for federal oversight of the organ transplant system. The Health Resources and Services Administration (HRSA) and the Health Care Financing Administration (HCFA) within the Department of Health and Human Services (HHS) currently administer programs related to organ transplantation. HRSA also administers the contract for the National Marrow Donor Program for which the Transplant Amendments Act of 1990 established standards.

We examined FDA's regulation of human tissue intended for transplantation, the agency's December 1995 draft document on the regulation of placental and umbilical cord blood stem cell products intended for transplantation, and the agency's proposed approach for the regulation of cellular and tissue-based products, as well as guidance from FDA and the Centers for Disease Control and Prevention (CDC) on screening donors of human tissues.² We obtained information on FDA's guidance on inspections for human tissue, summaries of findings on inspections, and memoranda relating to tissue donation and viral testing of donors. We met with officials from FDA and all the relevant industry associations to obtain their views on the regulation of tissue banking. We also collected information on state regulations and trade association standards and reviewed them for variations and gaps between federal, state, and private entities in the oversight of human tissue.

We interviewed representatives of and made site visits to the full complement of the types of tissue facilities within the scope of our study, including musculoskeletal facilities and processors, eye facilities, reproductive facilities, and facilities that collect, process, store, or transplant peripheral and umbilical cord blood stem cells. We observed tissue processing and infectious disease controls and reviewed documents relating to donor screening and standard operating procedures. We attended technical conferences and examined the scientific literature on the collection and processing of tissues, infectious and noninfectious complications from tissue transplantation, and variations in human tissue practices in order to obtain information on generally accepted practices and potential safety problems from tissue transplantation.

We conducted our review from November 1996 to September 1997 in accordance with generally accepted government auditing standards.

Results in Brief

FDA is just now expanding its oversight to improve tissue-banking safeguards in the growing field of tissue-based therapies. FDA's regulation, part of which will not be fully effective until January 26, 1998, specifies minimum medical screening and infectious disease testing and the maintenance of documentation for these activities and provides for retaining, recalling, or destroying human tissue for which such documentation is not available. FDA has also proposed a regulatory approach that is much broader in scope than the current regulation. Still in

²The December 1995 draft document was superseded by the proposed approach for tissue and cellular-based products.

its formative stages, it describes a risk-based approach that industry has generally received well. FDA plans to codify it iteratively over a period of years. Meanwhile, FDA's regulatory authority is limited to the requirements relating to the transmission of human immunodeficiency virus (HIV) and hepatitis B and C.

We found a number of safety problems that are not controlled under the current regulation and that will remain unsolved until future regulations are put into effect. Some of these problems are addressed in FDA's proposed approach, others are not addressed, and still others are addressed but not adequately.

FDA's proposed approach would alleviate three safety problems not covered by current regulation. First, because the current regulation does not require facilities to register with FDA, the agency has no universal registry of tissue facilities currently operating in the United States. As a result, FDA could not disseminate to all tissue banks critical information in a public health emergency that might affect the safety of transplanted tissues. FDA officials have stated that their agency does not plan to conduct routine annual inspections of tissue facilities for lack of resources, but the agency does plan to conduct some inspections.³ Without requirements for registration, FDA cannot identify the universe of tissue facilities that may warrant inspection or need to be notified. Second, the current regulation does not cover reproductive tissue or stem cell facilities. Although such tissues can transmit infectious diseases, these facilities are not required to abide by the current regulation for infectious disease control that covers musculoskeletal facilities and eye banks, nor will FDA be routinely inspecting these facilities. Third, we found numerous instances of misleading and false advertising in private cord blood banking; FDA is not currently regulating such product claims but would do so under the proposed approach.

We also found two problems that FDA does not address in the current regulation or in the proposed approach. First, some facilities obtain informed consent after infant delivery, raising safety and ethical concerns about cord blood from mothers who may not have received prenatal care and who are screened for high-risk behavior postcollection. Requesting consent after collection also does not provide expectant mothers with information and opportunity to make a decision before a procedure is performed. Second, although reproductive tissues and stem cells could

³For fiscal year 1998, FDA has planned 44 inspections of tissue facilities using a total of 2.8 full-time-equivalent staff.

introduce genetic diseases to recipients, FDA has no current or proposed requirements for disclosing to recipients whether genetic tests have been performed on these products.

We also found four instances in which FDA's proposed approach inadequately addresses potential safety problems not covered in the current regulation. First, facilities are not currently required to report errors or accidents that result in the distribution of unacceptable tissues or to report adverse events associated with the transplantation of human tissue.⁴ The proposed approach would require recording and investigating errors and accidents but no reporting to FDA. Without a requirement to report serious errors and accidents, FDA is missing an opportunity to target facilities that may need additional oversight.

Second, the current tissue-tracking system is inadequate to notify recipients who receive tissues later deemed to have been unsuitable for transplantation. Yet, the proposed approach only minimally mentions tracking tissues as good tissue practices and then only in respect to controlling disease transmission. Third, the proposed approach would require premarket submissions to FDA for certain tissues and cellular-based therapies that are to be used in an unrelated recipient (unrelated allogeneic). As a matter of policy, FDA would not require premarket submissions when cells or tissues were to be used in the person from whom they were obtained or in a close blood relative of that person (related allogeneic). This dichotomy ignores the similar risks from unrelated and related allogeneic transplantation.

Fourth, we found few processing techniques that tissue facilities had validated and FDA had evaluated; some nonvalidated processing techniques are known to adversely affect the safety and effectiveness of tissues. FDA has proposed that certain tissue products (for example, those that are more than minimally manipulated or nonhomologous) be subject to premarket approval and that FDA evaluate processing techniques used on these products in the course of reviewing premarket applications. But for the minimally manipulated tissue products that were the focus of our

⁴Presently, FDA regulations require licensed manufacturers of biological products to promptly notify FDA of errors or accidents that may affect the safety, purity, or potency of any product (21 C.F.R. 600.14). These regulations do not apply to tissue banks because no licensing is required. However, FDA has published a proposed rule that would require unlicensed blood facilities to report all errors and accidents. Adverse events that are serious or unexpected must be reported to FDA by the licensed manufacturer of biological products within 15 days of initial receipt of information. "Serious" means an adverse experience associated with the use of a biological product that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. "Unexpected" means an adverse biological product experience that is not listed in the current labeling of the product (21 C.F.R. 600.80).

review, the proposal would require only that the validation of the procedure be documented and available when FDA inspects facilities engaged in such activities. Because FDA does not plan to conduct routine inspections of tissue facilities, inspectors may have few opportunities to evaluate the different procedures that tissue facilities use.

Background

The term “tissue” covers a wide range of products used for many medical purposes. Traditionally, most human tissue used in medicine comprised such body components as skin, bone, corneas, and heart valves that were transplanted for replacement purposes as well as semen and ova implanted for reproductive purposes. In recent years, scientists have developed innovative methods of manipulating and using human cells and tissues for therapeutic purposes. For example, in what is known as somatic cell therapy, scientists are studying the use of human cells that have been manipulated in the laboratory to treat viral infections, Parkinson’s disease, diabetes, and other diseases and conditions. Other tissue research includes the use of blood from the placenta and umbilical cord to treat leukemia and other diseases.⁵

Two events in the early 1990s initiated concern about the safety of human tissue recovered for transplantation. The first was the transmission of the human immunodeficiency virus from a donor to a number of recipients of the donor’s organs and fresh-frozen bone tissue. The other event was the importation from foreign countries of human tissue for which there was no record of source or testing for infectious diseases. As a result of these events, FDA issued interim regulations on December 14, 1993, to help prevent the transmission of HIV and hepatitis B and C. This action was taken under section 361 of the Public Health Service (PHS) Act (42 U.S.C. 264), which authorizes the secretary of HHS to make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the United States or from state to state. The interim regulations provided for donor screening,

⁵Human blood contains a variety of cells tailored to specific functions. Erythrocytes, or red blood cells, transport life-sustaining oxygen throughout the body. Platelets arrest bleeding by promoting clotting. White blood cells, which include lymphocytes, monocytes, and neutrophils, form the immune system that guards an individual against attack by foreign tissue, viruses, and other microorganisms. All these cells develop from a “master cell,” the hematopoietic stem cell, which is found in the bone marrow and circulates in blood vessels throughout the body and in umbilical cord blood. Stem cells can divide to form more stem cells or they can go through a series of divisions by which they become fully mature blood cells. Most blood cells mature in the bone marrow. However, some white blood cells (lymphocytes) complete their maturation in the thymus, spleen, or lymph nodes. Injury to the stem cells—from chemotherapy, radiation, or disease, for example—can cripple the immune and blood production systems. The transplantation of stem cells can be used to treat people who have sustained such damage, such as those with cancer, aplastic anemia, and autoimmune disorders.

documentation of testing, FDA inspections of tissue facilities, and the recall of potentially unsafe tissue, but they were limited in the types of tissue they covered.

On July 29, 1997, FDA issued a final rule (to become effective January 26, 1998) for the regulation of human tissue intended for transplantation. The rule requires facilities engaged in the recovery, screening, testing, processing, storing, or distributing of human tissues to ensure that specified minimum required medical screening and infectious disease testing are performed and that records documenting screening and testing for each human tissue are available for FDA's inspection. The rule also contains provisions for retaining, recalling, or destroying human tissue for which appropriate documentation is not available. However, the rule does not cover reproductive tissue and stem cells.

In concert with the final rule, FDA issued guidance for industry for screening and testing donors of human tissue intended for transplantation. This document represents FDA's current thinking on screening and testing donors and does not bind FDA or the public to its recommendations. Tissue facilities can choose to follow this guidance or alternatives. The document outlines recommended tests and algorithms for accepting donors and gives information pertaining to screening donors to determine their acceptability.⁶

CDC has also set forth voluntary guidelines for screening and testing for HIV and hepatitis B and C. In 1994, CDC published a guideline on preventing the transmission of HIV through the transplantation of human tissues and organs. The guideline outlined recommendations on donor screening, donor testing for infectious diseases, laboratory and other medical exclusionary criteria for donors, record keeping for tracking recipients and tissues, testing recipients, and recalling stored tissue.⁷ In 1991, a Public Health Service interagency guideline was published covering issues relating to the screening of donors of blood, plasma, tissues, organs, and semen for evidence of hepatitis B and C that included information on screening, testing, medical evaluations, and counseling.⁸

⁶FDA, "Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation," Washington, D.C., July 1997.

⁷CDC, "Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs," Morbidity and Mortality Weekly Report, Vol. 43 (RR-8) (1994), pp. 1-17.

⁸CDC, "Public Health Service Inter-Agency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues, and Semen for Evidence of Hepatitis B and Hepatitis C," Morbidity and Mortality Weekly Report, Vol. 40 (RR-4) (1991), pp. 1-23.

Several industry associations are also involved in standard setting, and some conduct inspections. These include the American Association of Blood Banks (AABB), the American Association of Tissue Banks (AATB), the American Society for Reproductive Medicine (ASRM), the Eye Bank Association of America (EBAA), and the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT).

FDA has also circulated for public comment a proposed approach to the regulation of human cellular and tissue-based products that would provide oversight for the wide spectrum of cellular and tissue-based products that are marketed now or envisioned for the future.⁹ FDA plans to implement this approach iteratively, so it may be many years until the entire framework has the force of law. Broad in scope and ambitious in intent, the proposed approach is still in its formative stages and its final form is uncertain.

Below we present information on the different processes between when a prospective donor is identified and when human tissue can be transplanted. (More detail is given in appendix I.) We also outline the role of industry associations and state regulations relating to human tissue.

Processes

CDC has estimated that more than 400 facilities bank or process several hundred different types of human tissue.¹⁰ Some tissue facilities procure their own tissue and process it themselves. Other tissue facilities procure their own tissue but have it processed by an outside entity and then receive the tissue back from the processor for distribution to their clients (that is, hospitals and dentists). Some facilities receive tissue from other facilities for processing.

An assessment of tissue suitability is based on an extensive medical, sexual, and social history completed by the next of kin of a cadaveric donor. Living donors complete their own histories. The tissue of donors who meet all acceptance requirements is retrieved under aseptic or

⁹FDA's notice regarding its proposed approach to regulation of cellular and tissue-based products was published in the March 4, 1997, Federal Register. The approach does not encompass whole organs or minimally manipulated bone marrow (both of which are regulated by HRSA) or transfusable blood products (for example, whole blood, red blood cells, platelets, and plasma), which FDA already regulates under the Food, Drug, and Cosmetic Act and the Public Health Service Act. The approach also does not encompass other FDA-regulated tissue-related products, such as tissues derived from animals, products used in the propagation of cells or tissues, or products extracted from cells or tissues (such as human milk, collagen, or growth factors).

¹⁰A tissue bank is any facility that engages in recovering, screening, testing, processing, storing, or distributing human tissue intended for transplantation.

otherwise clean techniques and quarantined until a blood sample sent for infectious disease testing for HIV and hepatitis B and C shows that the tissue is safe.¹¹ Table 1 outlines the infectious diseases that have been transmitted by human tissue.

Table 1: Infectious Diseases Transmissible Through Human Tissue

Tissue	Infectious disease
Bone	Hepatitis, HIV, bacteria, tuberculosis
Skin	HIV (?) , bacteria, cytomegalovirus (?) ^a
Cornea	Hepatitis, bacteria, rabies, Creutzfeldt-Jakob disease, ^b fungus, herpes
Reproductive tissue ^c	Hepatitis, HIV, cytomegalovirus, human T-cell lymphotropic virus, ^d sexually transmitted diseases
Stem cells ^e	Hepatitis, HIV, cytomegalovirus, ^a human T-cell lymphotropic virus, ^d syphilis

^aCytomegalovirus belongs to the herpes virus group and is acquired by respiratory or sexual contact or from blood component or tissue or organ allografts. At this time, it is unclear as to whether HIV or cytomegalovirus can be transmitted by skin.

^bCreutzfeldt-Jakob disease leads to a degenerative neurologic disease that manifests as progressive dementia and death.

^cDiseases denoted in this table for reproductive tissue are based on those that ASRM testing standards require. Bacteria are likely transmissible.

^dHuman T-cell lymphotropic virus (HTLV) is similar to HIV in the manner in which it replicates itself. It has been associated with adult T-cell leukemia and tropical spastic paraparesis, or HTLV-I-associated myelopathy.

^eDiseases denoted in this table for stem cells are based on those that FAHCT testing standards require. Bacteria are likely transmissible.

Source: Adapted from T. Eastlund, "Infectious Disease Transmission Through Cell, Tissue, and Organ Transplantation: Reducing the Risk Through Donor Selection," *Cell Transplantation*, Vol. 4 (1995), p. 457.

Each donor is assigned a unique identification number to facilitate tracing tissues during processing and distribution. Processing procedures vary by tissue type. Some tissues undergo procedures to remove or inactivate viruses; others do not. Tissues that can be processed and sterilized include bone, tendons and cartilage, and fascia.¹² These procedures can be

¹¹AATB also recommends testing for human T-lymphotropic virus, syphilis, and bacteria. In addition, living donors are tested at the time of donation and 6 months later to ensure catching any infection too new to be detected by the first test. EBAA does not require testing for human T-lymphotropic disease or syphilis. Semen donors and donors of umbilical cord blood are tested for hepatitis B core antibody, an indication of past hepatitis B infection and potential high-risk behavior. Maternal umbilical cord blood donors are tested for cytomegalovirus, a highly prevalent and usually benign virus that is particularly dangerous for the immunocompromised patients who receive cord blood.

¹²Fascia is a sheet of connective tissue covering or binding together body structures.

employed on such tissues because they can function even though they are rendered acellular and nonviable. Cornea, skin, stem cells, and semen cannot undergo such processing because they contain viable cells that could be damaged.

All tissues are stored in containers capable of withstanding appropriate storage conditions and are labeled with the tissue identification number, tissue facility name and address, expiration date (if applicable), acceptable storage conditions, disinfection or sterilization procedure and preservatives or potential residues of processing (if applicable), and an instruction to “see the package insert.” The package insert supplies additional information for the health professional, including possible contraindications and adverse reactions. Distribution information is recorded for tracking in the event that transplanted tissue is found to have come from a donor who is later identified as positive for an infectious disease.

The Role of Industry Associations

AATB has standards and an accreditation program for its members. AATB currently accredits 60 tissue facilities, while another 40 to 60 are not accredited.¹³ AATB inspects its member institutions for compliance with the standards. AATB has recently hired an inspector to inspect its member institutions, and this inspector has no affiliation with any tissue facility. Before this, tissue facilities inspected one another for accreditation purposes. AATB standards outline procedures for tissue facilities in the areas of record management, screening, tissue retrieval, processing, quarantine, labeling, storage, and distribution. Also, AATB standards have specific information relating to musculoskeletal, skin, semen, and cardiovascular facilities.

EBAA has an accreditation program and standards for its members, and the American Academy of Ophthalmology independently reviews EBAA’s standards. These standards cover such issues as training and certification of eye-banking personnel, donor screening, procurement and preservation procedures, tissue evaluation, storage, labeling, and distribution. EBAA has 110 members; some eye banks are not members. As with AATB, EBAA inspects its member institutions.

¹³There are also about 110 eye banks, 100 reproductive tissue banks, and about 100 surgical bone banks. This latter group has declined recently as these banks were usually in hospitals that stored bone from surgical bone procedures, such as from living donors who had hip replacement surgery, whereby the extracted femoral head could be used for other patients.

The approximately 315 individual members of ASRM are mostly reproductive medicine practitioners. ASRM is a professional organization but it does not certify or accredit sperm banks. There are about 150 assisted reproductive technology programs in the United States.¹⁴ CDC estimates that there are about 100 semen banks and an undetermined number of smaller semen banks based in hospitals or the offices of individual physicians.¹⁵ ASRM, in conjunction with the College of American Pathologists, sets standards for the accreditation of reproductive laboratories that include requirements for laboratory personnel, resources and facilities, and quality control and assurance. Approximately one-third of the reproductive laboratories in the United States are accredited. ASRM also has draft guidelines for therapeutic donor insemination and a guideline for oocyte donation. The latter includes appendixes on the minimal genetic screening for gamete donors and psychological assessments for anonymous and known oocyte donors. Guidelines for gamete donation were made final in 1993.

FAHCT has initiated a voluntary standard-setting inspection and accreditation program that encompasses all phases of hematopoietic stem cell collection, processing, and transplantation. It is a nonprofit organization developed by the International Society of Hematotherapy and Graft Engineering (ISHAGE) and the American Society for Blood and Marrow Transplantation (ASBMT) for self-assessment and accreditation in the field of hematopoietic cell therapy.¹⁶

¹⁴Assisted reproductive technology programs are involved in such practices as in vitro fertilization, gamete intrafallopian transfer, and zygote intrafallopian transfer. These are procedures performed to assist couples who have infertility problems to conceive children. For example, embryology laboratories are an integral part of in vitro fertilization, gamete intrafallopian transfer, tubal embryo transfer, and zygote intrafallopian transfer programs. These are collectively known as assisted reproductive technologies. Embryology laboratories are not referral laboratories but maintain specific affiliation with a physicians' group. They perform some of the following activities: examination of follicular aspirates with oocyte identification; oocyte quality and maturity grading; sperm preparation; insemination of oocytes; determination of fertilization and zygote quality evaluation; and oocyte, embryo, and sperm cryopreservation. Andrology laboratories, in contrast, perform activities such as semen analysis, semen biochemical tests, tests for sperm survival, sperm viability and integrity, sperm antibody testing, preparation of sperm for intrauterine insemination, and sperm cryopreservation.

¹⁵A single anonymous semen donation can be divided into several (four to eight) samples, and, industrywide, about one of every eight potential donors is accepted. Some sperm banks accept only 3 to 5 percent of the applicants, and even those that are accepted as donors often produce donations that are not acceptable (at one sperm bank, only 33 percent of the donations are accepted).

¹⁶ISHAGE was formed in 1992 as a professional society representing scientists and physicians working in the area of hematopoietic stem cell graft manipulation. It has more than 900 members representing all the major bone marrow and stem cell transplant centers in the world. It developed the first draft of the Standards for Hematopoietic Cell Collection and Processing. ASBMT was formed in 1993 as a professional organization representing physicians and investigators involved in the clinical conduct of hematopoietic progenitor cell transplantation. It has more than 800 members and developed the first draft of the Clinical Standards for Hematopoietic Cell Transplantation.

FAHCT has established quality standards for medical and laboratory practice in hematopoietic cell transplantation. They cover topics such as donor evaluation and selection, collection procedures, processing, cryopreservation, labeling, storage, transportation, and records management. FAHCT plans in the near future to conduct inspections and accredit programs that will encourage health institutions and facilities performing hematopoietic cell transplantation to voluntarily meet its standards. Recognition of compliance with the standards will result in certificates of accreditation. Additionally, AABB has standards on hematopoietic progenitor cells (that is, stem cells) that cover issues relating to donor selection, collection, cell processing, laboratory testing, labeling, storage, and distribution.

The National Marrow Donor Program (NMDP) compiles statistics on the number of transplants from bone marrow, peripheral stem cells, and cord blood stem cells. The International Bone Marrow Transplant Registry collects data on allogeneic transplants performed worldwide. Information on peripheral and cord blood stem cell transplants has been collected since 1990. Transplants that NMDP facilitates must be reported to this registry; otherwise, reporting is voluntary. About 40 to 50 percent of the transplants are reported.

In October 1996, NHLBI announced the first multicenter study of umbilical cord blood stem cell transplants from unrelated, newborn donors. The 5-year \$30 million study is designed to show whether cord blood transplantation is a safe and effective alternative to bone marrow transplantation for children and adults who have a variety of cancers, blood diseases, and genetic disorders. The cord blood units will be collected at three facilities. The transplants will be conducted at seven centers using standard protocols for enrolling patients, preparing them for transplant, and treating them after transplant. A data-coordinating center will identify the units for transplant as well as collect the data from the study.

Table 2 provides an overview of the relevant facts and figures associated with tissue banking in the United States today.

Table 2: Tissue Banking Facts and Figures

Types of tissue	Number of donors annually	Estimated number of banks	Estimated number of recipients annually	Industry association
Musculoskeletal: bone (whole, crushed, chips, demineralized powder), cardiovascular, cartilage, skin, tendon	5,500	About 100; 2 largest collect 50-55%; 6 others collect 30-45%	350,000	AATB
Eye tissue: cornea, sclera	40,000-45,000	110	40,000-45,000	EBAA and American College of Ophthalmology
Reproductive: embryo, oocyte, semen	Unknown	100 semen banks, 150 assisted reproductive technology facilities, 300 laboratories	Semen = 200,000; embryo= 2,500	ASRM and American College of Pathology
Stem cells Umbilical cord blood	Unknown	20-50 collect umbilical cord blood; 6 private banks; 6 public banks ^a ; about 15 facilities have performed cord blood transplants	250 (U.S.), 500 (worldwide); 75% are unrelated allogeneic ^b	AABB, ASBMT, FACHT, ISHAGE
Peripheral		Unknown number	700 (U.S.), 2,000 (worldwide); most are related allogeneic	

^aThe number given for private banks is based on those that have advertised through the Internet as of August 22, 1997. An unknown number of private physicians may be collecting and storing cord blood stem cells. The number given for public banks is based on information obtained from NHLBI.

^bTotal transplants to date.

State Regulations

Several states have promulgated regulations on specific standards required at particular types of tissue facilities. For instance, some states require sperm banks to register and to be inspected by state health departments, while other states have guidelines on the interpretation of tissue donor screening test results and the processing and storage of stem cells.

CDC is currently establishing prototype regulations from which states could model their own regulations on reproductive tissues. CDC was mandated to do this by the Fertility Clinics Success Rate and Certification Act of 1992. CDC officials stated that the model laboratory certification program will closely mirror existing laboratory accreditation procedures formulated by the College of American Pathologists laboratory accreditation program. In addition to requiring CDC to establish model regulations, the act required

assisted reproductive technology programs that assist infertile couples to report pregnancy success rates to CDC. Presently, California, Florida, Minnesota, and New York have regulatory programs or are working on legislation for reproductive tissue.

Several states have also enacted three categories of corneal removal laws: (1) implied consent, in which corneas may be released to an eye bank when it is a medical examiner's or coroner's case, an autopsy is required, release would not interfere with a subsequent investigation, and there is no known objection by next of kin; (2) diligent or reasonable search, in which an effort must be made to contact next of kin within a specific time period before release of corneas; and (3) consent only, in which release is possible only when authorized next of kin consent has been obtained. According to EBAA, 12 states and Puerto Rico have implied-consent laws, 9 states have diligent search laws, and 6 states have consent-only laws.

Overview of Current Regulation and Proposed Approach

FDA's current regulation on human tissue intended for transplantation covers several areas of tissue collection, processing, and storage, all relating to the control of hepatitis B and C and HIV transmission. These include (1) donor screening and testing; (2) requirements for written procedures for testing for infectious disease and obtaining, reviewing, and assessing the medical records of donors; (3) record keeping; (4) quarantining requirements; (5) FDA authority to inspect tissue facilities; (6) importation of human tissue; and (7) retention, recall, and destruction of human tissue.

The proposed approach to the regulation of tissue and cellular-based therapies represents a move toward forward-thinking regulation of a diverse and rapidly advancing field. It is less prescriptive than traditional FDA regulation and it has generally been well received by industry. Although it is clearly open to broad interpretation, it would expand the current FDA oversight to include reproductive tissues and stem cells. The approach would focus on three main areas: (1) preventing unwitting use of contaminated tissues with the potential for transmitting infectious diseases, (2) preventing improper handling and processing that might contaminate or damage tissues, and (3) ensuring that clinical safety and efficacy are demonstrated for tissues that are highly processed (more than minimally manipulated), used for other than their normal function (nonhomologous), combined with nontissue components, or used for metabolic purposes.

The Proposed Approach Addresses Certain Omissions in Current Regulation

We have three concerns about omissions in the current regulation that FDA has identified and plans to address under its proposed approach: (1) lack of registration of tissue facilities, (2) some types of tissue facilities not covered under the current regulation, and (3) misleading and false advertising in cord blood banking. However, because the proposal will be promulgated iteratively, these omissions may remain for the foreseeable future.

Facilities Not Required to Register

Unlike in other industries that FDA regulates, such as blood and implantable medical devices, FDA does not have an accurate list of tissue facilities in the United States because these facilities have not been and are not now required to register with FDA. Therefore, FDA can neither notify all tissue facilities as potential public health threats arise nor plan inspections from a complete registration of tissue facilities.¹⁷ FDA recognizes this deficiency and is drafting a regulation that would require registration.

FDA previously inspected tissue facilities “for cause” but now intends to conduct a small number of routine inspections. According to data obtained from FDA on its inspection activities, the agency conducted 14 inspections in 1997. With resources of 2.8 full-time staff equivalents, the agency expects in fiscal year 1998 to inspect 44 of the approximately 200 known tissue facilities now covered by the current regulation. Adding reproductive and stem cell facilities and others currently not identified would increase FDA’s inspection burden.

FDA officials have stated publicly that they will also rely on industry associations to monitor their members. However, among the approximately 400 known tissue facilities, fewer than half, or about 170, are accredited by industry associations. A complete registry of facilities would include nonmembers of industry associations and those that failed accreditation.

While industry associations recommend standards for their member institutions, some facilities do not abide by them. For example, AATB standards state that anonymous semen donors should be younger than 40 years of age. However, some sperm banks collect donations from men older than 40. AATB standards also state that semen is not to be distributed to private individuals without a physician’s written order, but according to

¹⁷Identification techniques that FDA has employed include (1) asking known tissue banks about others that they compete with for donors, (2) receiving assistance from a local coroner or medical examiner to identify tissue facilities that procure tissue, and (3) consulting local telephone directories.

some in the industry, some sperm banks do, in fact, sell semen samples directly to private individuals. Furthermore, officials from ASRM stated that each semen donor is limited to 10 resulting pregnancies to limit the possibility of genetic offspring unknowingly intermarrying. However, some sperm banks do not abide by this limit.

To date, FDA has inspected approximately 80 tissue banks and has issued 15 notices for the recall of tissues at 10 tissue facilities. FDA has also issued letters of opportunity for voluntary corrective action.¹⁸ For example, in a December 1996 letter, FDA notified one EBAA-accredited eye bank that it had procured eye tissues from 43 donors between December 1993 and January 1994 that were subsequently processed, distributed, and transplanted without any testing for anti-HIV 2. FDA has also performed an initial analysis of 30 Form 483s issued to 27 tissue facilities between January 1994 and June 1996 that resulted in 216 observations.¹⁹ Approximately half of these observations were related to section 1270.5(e) of the interim rule, which stated that it should be determined that a donor of tissue intended for transplantation is suitable, including ascertaining the donor's identity and adequately completing and recording relevant medical histories to ensure freedom from risk factors for or clinical evidence of hepatitis B, hepatitis C, or HIV infection.

Potential problems among association nonmembers and those that do not abide by industry standards, as well as clear problems identified in FDA initial inspections, illustrate that FDA inspection is necessary to maintain the safety of human tissue intended for transplantation. Only through registration of all tissue facilities will FDA have an adequate means by which to plan its inspection activities. Furthermore, while industry inspections can augment this process, only FDA has the legal authority, under the Federal Food, Drug, and Cosmetic Act, to impose actions such as injunctions and seizures of certain products.²⁰

¹⁸The purpose of such correspondence is to provide facilities with the opportunity to implement voluntary corrective action to bring a facility and its operations into compliance with the current regulation. Such action may include, but is not limited to, notifying physicians of medical risks involved with the tissues that are referenced in the letter.

¹⁹Form 483 allows FDA inspectors to attach inspection observations to an establishment inspection report that is thought to violate an FDA regulation.

²⁰This applies only to tissue products that are more than minimally manipulated, are for nonhomologous use, are combined with noncellular or nontissue components, or are for metabolic use other than reproduction except when used autologously or in a close family member. For other minimally manipulated tissues that are regulated solely under section 361 of PHS, the authorities for injunctions under section 302 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 332) and seizures under section 304 of that act are not available.

Some Facilities Are Not Covered by Current Regulation

The current regulation does not cover facilities that collect, store, process, or distribute reproductive tissues or stem cells. Specifically, these facilities are not required to adhere to the requirement for infectious disease testing nor does FDA have direct authority to inspect these facilities for compliance with the current regulation.²¹ Reproductive tissues and stem cells can transmit hepatitis, HIV, human T-cell lymphotropic virus (HTLV), cytomegalovirus, and sexually transmitted diseases. Because work in both kinds of tissue is expanding, this represents a significant gap in FDA oversight. FDA recognizes the safety implications of this omission and would begin its oversight of these tissue facilities by including them in registration requirements.

Some Umbilical Cord Blood Banks Use Misleading and False Advertising

Little is known about the type and level of information that private cord blood facilities present to expecting parents, either in writing or orally. FDA has periodically monitored but not regulated this industry's advertising practices.

Techniques to collect, process, store, and transfuse cord blood are not well established, but this fact is not emphasized to prospective parents. If provided at all, the extremely low probability of ever requiring the cord blood unit for transplantation into the child or a family member is rarely, if ever, completely portrayed. Nor are parents always told of other sources of stem cells, such as peripheral blood and bone marrow, that can be collected and transplanted when they are needed. Current scientific knowledge suggests that umbilical cord blood stem cells are less likely to initiate graft versus host disease (GVHD) in a recipient than bone marrow and, perhaps, peripheral stem cells.²² However, new techniques and immune suppression therapies are constantly improving GVHD rates, thus increasing the likelihood that the future transplant needs of a family could be met without the costly collection and storage fees associated with cord blood. Moreover, because GVHD rates associated with the transplantation of unrelated—even highly genetically mismatched—cord blood stem cells from public banks appear to be so low, the need for a highly genetically matched family member is not the gravely important issue that it is in the transplantation of bone marrow stem cells.

²¹FDA's regulation requiring facility registration, currently in draft, will include reproductive and stem cell facilities. Subsequent regulations will cover good tissue practices and infectious disease testing for these facilities.

²²In GVHD, donor lymphocytes engraft and multiply in the recipient, reacting against the "foreign" tissues of the recipient. When donors and recipients are highly "matched" for antigens, GVHD is lessened.

Table 3 illustrates the type of misleading and false information that prospective parents can find on the Internet as they research decisions to store their unborn child's cord blood. For example, while one company claims that "autologous transplants are the most common type of transplant performed," there have not, in fact, been any published reports of autologous cord blood transplants in patients for treatment of a malignant disease. Moreover, scientific controversy surrounds the use of a young child's own stem cells to reconstitute a diseased immune system. We found unsubstantiated and exaggerated claims, both implied and explicit, in four areas relating to umbilical cord blood: its safety relative to bone marrow transplantation, scientific research establishing the feasibility and efficacy of transplanting it, the number and type of transplants to date, and the state of the art of collecting, processing, and storing it.

Table 3: Misleading and False Information About Umbilical Cord Blood on the Internet

Information ^a	Correction
"It has the added advantage of being 'privileged' or unexposed to most diseases."	Cord blood is at risk for any disease of the mother, who, as an adult, has risks equal to those of any other adult who might donate bone marrow.
"Cord blood is rarely contaminated by viruses such as cytomegalovirus or Epstein-Barr virus that can cause serious problems for the transplant patient."	
"Cord blood stem cells are not infected by HIV"	
"Because they are captured immediately after birth, they are much less likely than stem cells found in an adult's bone marrow to contain contaminating viruses."	
"very low risk of transmissible infectious diseases"	
"As a result of numerous preclinical and clinical studies supporting the feasibility and efficacy of umbilical cord transplantation"	The feasibility and efficacy of umbilical cord blood transplantation have not been scientifically established. The National Institutes of Health is just beginning to conduct the first true clinical trial, which will be completed in 5 years. Cord blood has been used to treat a very limited number of diseases. Its comparability to bone marrow has not been clinically established.
"Cord blood can be used to treat any cancer or genetic disease that is currently treatable by bone marrow transplantation."	
Compared to bone marrow recipients, "cord blood transplant recipients have a higher survival rate, a higher quality of life after transplant and less frequent hospitalization due to complications such as graft vs host disease."	
"it has been found that cord blood stem cells are much more proliferative than bone marrow stem cells"	
"Already, cord blood stem cells have been used in hundreds of cancer, blood and immune system treatments with a success rate of 85%."	We are unaware of any data supporting this statement.

(continued)

Information ^a	Correction
"an individual's own cord blood offers an appropriate source of transplantable cells, furthermore, autologous transplants are the most common type of transplant performed."	To date, no autologous cord blood transplants have been conducted to treat a malignant disease.
"There is no risk to the mother or baby from collection."	While risks are probably extremely low, the collection and specimen preparation require the attention of the attending physician or nurse when his or her attention is normally on the mother and baby.
"All reagents used in processing are FDA approved."	FDA has not approved any processing reagents for use in preparing stem cells.
"Stem cells can be cryogenically frozen or stored for an indefinite period of time."	Cord blood stem cells have been stored for 15 years; however, the oldest unit used in a transplant was stored for less than 5 years. It is not currently known how long cryogenically frozen stem cells remain viable.
"1 in 100 blood recipients [receiving 5 units] will contract various forms of hepatitis transmitted through blood."	The risk of hepatitis B to a recipient of 5 units of blood is about 1 in 12,000; it is 1 in 1,800 to 1 in 20,000 for hepatitis C. ^b

^a Such information has been provided to prospective parents by private firms advertising on the Internet as recently as August 21, 1997.

^bG. Schreiber and others, "The Risk of Transfusion-Transmitted Viral Infections," *New England Journal of Medicine*, Vol. 334 (1996), pp. 1685-90, and *Blood Supply: Transfusion-Associated Risks* (GAO/PEMD-97-2, Feb. 25, 1997). The range for the risk estimate for hepatitis C is based on the possibility that there may be individuals with chronic infections who do not produce detectable seropositivity.

Clearly, consumers have the right to collect and store umbilical cord blood for personal use. However, they should also be protected from misleading or inaccurate information, and the risks and benefits of other therapies should be made known to them.

FDA officials are concerned about the types of information being provided to the public regarding umbilical cord blood and have engaged in discussions with the Federal Trade Commission regarding the regulation and monitoring of this industry. Under the proposed approach, FDA would provide some regulation of product claims for umbilical cord blood.

The Proposed Approach Does Not Address Certain Omissions in Current Regulation

We have two concerns about omissions in the current regulation that are not addressed in the proposed approach: (1) issues surrounding informed consent for cord blood and (2) the lack of requirements for the disclosure of genetic testing of reproductive tissues.

Obtaining Informed Consent After Collecting Umbilical Cord Blood Raises Safety and Ethical Concerns

The largest public cord blood facility that collects umbilical cord blood stem cells for use in unrelated allogeneic recipients usually obtains informed consent from the mother after the cord blood has been collected. This facility follows this practice because obtaining consent in advance can be highly problematic. For instance, some mothers do not receive prenatal care and, thus, do not afford the cord blood facility the opportunity to obtain informed consent before delivery. An FDA official stated that since the placenta and umbilical cord are normally discarded following delivery, these tissues typically become the property of the hospital. For other tissues removed and discarded (as in surgery), consent to collect portions for other uses is not generally required. Therefore, an argument can be made that consent is needed for umbilical cord blood testing and use but not collection.

Two safety concerns are raised when informed consent is not obtained until after collection. First, the health implications to recipients of umbilical cord blood from mothers who may not have received prenatal care are currently unknown. Second, an essential safety control is to ask the mother a series of screening questions regarding her behavior and exposure to disease. A new mother might not answer truthfully questions on high-risk behavior (such as illicit drug use) that could otherwise result in removing her newborn from her care.

The public cord blood bank that obtains consent after collection is operating under an FDA-approved investigational new drug (IND) protocol and has obtained institutional review board approval from the hospital where the cord blood is collected. The current cord blood banking protocols under FDA-approved INDs will provide the opportunity through data collection to assess the safety and risks of seeking informed consent after cord blood has been collected. Until these analyses have been conducted, the safety of seeking consent after delivery remains unknown.

There is also an ethical concern in obtaining consent after collection. A recent consensus statement from the Working Group on Ethical Issues in Umbilical Cord Blood Banking noted that informed consent should be obtained before procuring placental blood for transplantation because not obtaining consent runs counter to the explicit reasoning behind informed consent—that is, providing an individual with the information and opportunity to make a decision before a procedure is performed.²³

²³J. Sugerman and others, "Ethical Issues in Umbilical Cord Blood Banking," Journal of the American Medical Association, Vol. 278 (1997), pp. 938-43.

Obtaining consent before delivery affords the mother the opportunity to deliberate more fully on the decision before the birth.

The National Heart, Lung, and Blood Institute (NHLBI) multicenter study examining cord blood transplantation will require consent before delivery. AABB's accreditation requirements state that the informed consent of a blood, apheresis, or marrow donor must be obtained and documented before donation. However, FAHCT has provided for flexibility in obtaining informed consent after cord blood has been collected. FDA recommendations for blood donation note that informed consent should be obtained before each donation in language relating to potentially high-risk behavior. This allows the donor an opportunity to notify collection personnel and health care professionals with information that could protect them from infectious diseases.

Genetic Testing on Reproductive Tissues That Might Limit Transmission of Genetic Anomalies Is Not Disclosed

Neither FDA's current regulation nor its proposed approach has language on disclosure of genetic tests that have been performed on donors of reproductive tissues that, when transplanted, could result in the transmission of genetic anomalies. Without such disclosure, recipients of these tissues lack vital information that, if available, might alter their decision to use tissues from such donors.

Genetic anomalies in donated sperm or eggs can cause serious or fatal diseases. Donors may be unaffected carriers of these anomalies with no family history of such disease. Such genetic diseases arise when a child inherits an affected gene from both the mother and father. While some genetic diseases are more prevalent in certain ethnic and racial populations, the rise of interracial and mixed ethnic marriages makes these population distinctions less valuable as a screening tool (see table I.1).

Studies conducted to determine, retrospectively, whether new tests to detect cystic fibrosis would find previous donors to be carriers found that of 149 actual donors, 5 were heterozygous carriers of the mutation for cystic fibrosis. Also, 1 of 100 donor applicants was found to be a heterozygous carrier. The researchers determined that the chance was 1 in 16,100 that an individual who had no family history of cystic fibrosis and who used a DNA-tested donor would bear a child with the disease. They concluded that it is important for donor banks to perform genetic

screening for cystic fibrosis and that such screening “is a responsible policy that will eliminate most high-risk carriers.”²⁴

AATB standards state that donors should be tested for Tay-Sachs disease, thalassemia, sickle cell trait, or cystic fibrosis if indicated by their family history or ethnic background. However, since AATB accredits only six reproductive facilities, it is not known how often such testing is performed. Genes for some diseases, such as those discussed above, are determinative when both parents pass them on and their offspring have the disease. Other genes are not determinative, such as the recently discovered gene for breast cancer; scientists still do not know what it means to carry this gene. Some reproductive tissue facilities go beyond the AATB standards and perform chromosomal analyses and testing for the gene that has been implicated in breast cancer. Genetic testing is an emerging science, none of these tests are 100-percent accurate, and FDA has not approved or cleared them for the intended use of screening reproductive donors; therefore, FDA does not plan to require that such tests be performed. However, we believe that consumers should know, for informed decision making, which facilities conduct such testing to maximize the safety of their products and which do not.

Proposed Approach Does Not Adequately Address Certain Issues

Four issues not addressed in the current regulation are addressed in the proposed approach but in a manner that does not adequately eliminate potential safety problems: (1) the lack of error and accident reporting to FDA, (2) inadequate tracking systems, (3) the lack of safety and efficacy data on specific stem cell therapies, and (4) inadequate tissue-processing techniques.

Error and Accident Reporting Is Not Required

There are presently no federal requirements that tissue facilities maintain records for the reporting of errors and accidents or adverse events to FDA, even though this practice is required for similar types of industries such as blood banking. For example, the distribution of quarantined tissues or the inadvertent transplantation of tissue testing positive for infectious disease might go unreported.

The proposed approach would require the reporting of adverse events associated with infectious disease transmission but not errors and accidents. FDA officials believe that requiring facilities to record and

²⁴E. F. Fugger, Anne Maddalena, and J. D. Schulman, “Results of Retroactive Testing of Human Semen Donors for Cystic Fibrosis and Human Immunodeficiency Virus by Polymerase Chain Reaction,” *Human Reproduction*, Vol. 8 (1993), pp. 1435-37.

investigate errors and accidents without reporting to the agency even a subset of the most serious ones is sufficient to monitor the industry. In fact, FDA interprets section 361 of PHS (which authorizes regulations to control the spread of communicable disease) as authorizing regulations requiring the reporting of tissue failures based on problems associated with processing, among other events, because repeated tissue failures may require repeated tissue transplants, thereby increasing potential exposure to communicable disease. But because errors and accidents are often early warning signals of noncompliance or poor practices, FDA is missing an opportunity to identify tissue facilities that would benefit from additional FDA oversight. One recent FDA inspection found that a firm had distributed corneas before receiving test results showing that one cornea had tested positive for HIV.²⁵ The proposed approach, if implemented as written, would not require the reporting of incidents such as this one.

Current Tracking Systems Cannot Identify Recipients of Tissue Transplants

We found that FDA's tracking system for identifying recipients of transplants that may have been virally infected is incomplete. For example, when attempting to track recipients of a donor who tested negative on the first-generation hepatitis C test but positive on the second-generation test, researchers found that 1 of 16 grafts released for distribution from this donor was sent to a hospital that had no record of the graft.²⁶ This made it impossible to notify the recipient of this graft of his or her potential exposure to hepatitis C.

Additionally, a study conducted in 1993 by one tissue facility found that 23 percent of the hospitals that it surveyed had no tracking system. Another facility had only a 65-percent compliance rate for reporting the final disposition of tissues that it distributed.²⁷ A 1994 survey of 54 tissue facilities reported that only 34 percent of the respondents were always capable of identifying the patient who received their tissues, and only 10.5 percent routinely received feedback on tissue use from hospitals.²⁸

AATB standards state that the records management system of a facility should permit the reciprocal tracing of tissues from donors to those who

²⁵This cornea was later recalled and destroyed.

²⁶E. Conrad and others, "Transmission of the Hepatitis-C Virus by Tissue Transplantation," *Journal of Bone and Joint Surgery*, Vol. 77-A (1995), pp. 214-24.

²⁷Information presented at the June 20-21, 1995, FDA Workshop on Tissue for Transplantation and Reproductive Tissue: Scientific and Regulatory Issues and Perspectives, Bethesda, Md.

²⁸J. Protas, "A Study of the Tissue Procurement and Distribution System of the United States," draft, FDA contract #240-09-0048, October 1995.

receive them and back. Also, the standards state that upon discovering the need for recalling tissues, facilities should promptly notify all entities to whom affected tissue was distributed or dispensed. For this reason, some within the tissue industry have called for regulations requiring that receiving institutions or clinicians be responsible for keeping records of the final disposition of tissues so that tissue facilities can identify recipients of tissues that might be contaminated.

Moreover, a CDC guideline for preventing the transmission of HIV through the transplantation of human tissue and organs recommends that all facilities involved in the acquisition of tissues or organs from a single donor be able to communicate among themselves for the purpose of tracking tissues and organs to recipients who should be notified when HIV transmission is confirmed.²⁹

Imposing tracking requirements is not without precedent within FDA. Presently, the Center for Devices and Radiological Health has a tracking requirement for approximately 20 percent of the devices it regulates that is based on the potential for serious adverse health consequences. Specifically, section 519(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360i) requires that manufacturers track certain devices from the manufacturer through the distribution chain to the patient. Devices covered under this section include heart valves, vascular grafts, breast and penile implants, and pacemakers. This tracking permits manufacturers to directly notify patients of a recall when a problem has been identified. Similarly, blood facilities are required to track units from donors who subsequently test positive for HIV to the recipients of those units (C.F.R. 610.47(b)).

To date, however, a significant gap remains in the tracing of tissues. FDA officials stated that the proposed approach addresses this problem, but tissue tracking is mentioned in the proposed approach only as an example of good tissue practices and its role in the transmission of communicable diseases.³⁰

Stem Cell Therapies Are Not Yet Well Characterized

Under the proposed approach, tissues transplanted from one person to another for their normal function (homologous use) without undergoing extensive processing (minimal manipulation) would be subject to

²⁹CDC, "Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs."

³⁰See FDA's proposed approach, table 1.

infectious disease screening and testing, and to requirements for good tissue practices, but would not need FDA review or premarket approval.³¹ Thus, most processors of conventional and reproductive tissues would not be required to submit information about their products to FDA or to seek its permission to market those products.

The proposed approach would require premarket approval for tissues that were processed extensively (more than minimally manipulated), combined with nontissue components, used for purposes other than their normal function (nonhomologous use), or contained a metabolic mode of action. This latter category would include stem cells that were obtained for allogeneic use, defined in the proposed approach as unrelated allogeneic transplants. Stem cells that were obtained for autologous use or from a close blood relative (related allogeneic) would not require FDA approval.³²

A current moratorium on the requirement for IND and premarket approval applications allows the stem cell community time to collect information that may provide FDA with adequate data to promulgate standards. If sufficient data do not become available to establish processing and product standards after a specified period of time, stem cell products will be subject to IND and marketing application requirements. The approach notes that FDA intends to invite professional groups and individuals to submit data and standards that they believe would ensure the safety and effectiveness of stem cell transplantation. FDA intends to list in the Federal Register questions relevant for collecting data on volume, storage temperature limits, limits on microbial or other contamination, viable cell number, and functionality. In addition, FDA will request information on procedures for handling, transporting, storing, and thawing materials and for when and how contamination and viability testing should be carried out.

For several reasons, we are concerned about the demarcation that the proposed approach makes between unrelated allogeneic and related allogeneic donations. Efficacious collection, processing, and storing methods are not yet well characterized within the cord and peripheral blood stem cell community. The mitigation of this problem is not related to the source of stem cells (autologous, family-related, or unrelated

³¹Premarket approval includes an IND, or request for authorization from FDA to administer an investigational drug or biological product to humans. Such authorization must be secured before the interstate shipment and administration of any new drug or biological product that is not the subject of an approved new drug application or product license.

³²Close blood relative is defined in the proposed approach as a first-degree blood relative (that is, parent, child, or sibling).

allogeneic), even though the proposed approach makes a demarcation between the source of the stem cells and whether premarket approval should be required. Furthermore, the academic medical community considers the collection of data on the safety and efficacy of umbilical cord blood transplantation to be at the investigational phase. For example, a 1996 scientific research report of 18 allogeneic transplantations described its research as “a phase I clinical trial.”³³

Stem cells from umbilical cord blood are typically collected by attending obstetricians or nurses during delivery. Most collections are performed by medical personnel who have had no formal collection training and, indeed, may be collecting cord blood for the first time. Meanwhile, research has shown that different collection and processing techniques affect levels of bacterial contamination and the viability of cells.³⁴ For example, the rate of bacterial contamination was 3.3 percent for collections that used closed systems and 12.5 percent for collections that used open systems.

Cord-clamping time was also found to influence the volume of cord blood collection and, therefore, the potential to obtain more stem cells. However, many facilities instruct obstetricians to “clamp the cord as you normally would.” Additionally, the efficacy of separation procedures to obtain stem cells from the cord blood was markedly reduced when the cord blood samples were stored for more than 12 hours before separation. Cord blood collected for private banking is usually not processed before 24 or even 48 hours. The investigators also questioned the validity of some traditional methods of determining the potential for the collected cells to engraft sufficiently to restore a patient’s immune system.

Similarly, much is still not known about the optimal collection and assessment of viable stem cells from peripheral blood. Because the pluripotent hematopoietic stem cell has not yet been isolated, all current methods of measuring the efficacy of the collection and quality of

³³A phase I clinical trial is the earliest experimental stage for testing in humans. J. Wagner and others, “Successful Transplantation of HLA-Matched and HLA-Mismatched Umbilical Cord Blood From Unrelated Donors: Analysis of Engraftment and Acute Graft-versus-Host Disease,” *Blood*, Vol. 88 (1996), pp. 795-802.

³⁴F. Bertolini and others, “Comparative Study of Different Procedures for the Collection and Banking of Umbilical Cord Blood,” *Journal of Hematotherapy*, Vol. 4 (1995), pp. 29-36.

peripheral or cord blood progenitor cells are indirect.³⁵ Some studies have examined collection and processing methods to determine which ones yield more viable stem cells for transplantation, but investigators have noted that the protocols and procedures used to collect peripheral blood cells have not been standardized.³⁶

While some information points to greater success in transplants from related donors, the factors that influence the success of cord blood transplants are just emerging. For example, recent research has pointed out that patients who received cord blood from an unrelated donor had significantly lower estimates of survival at 1 year—29 percent versus 63 percent for recipients of related donors.³⁷ As with bone marrow transplants, greater success was achieved with a donor with identical human leukocyte antigen (HLA), which is more likely to occur with a related donor.³⁸ GVHD was different between HLA-matched and unmatched donors and recipients. GVHD occurred in 9 percent of 60 recipients of HLA-matched cord blood and in 50 percent of 18 recipients of mismatched cord blood. However, none of the GVHD cases were life-threatening. This study also found that for the 143 transplants examined at 45 participating centers, methods of collecting, cryopreserving, storing, and thawing cord blood varied widely. For example, the number of cells infused after thawing ranged from 7 million to 300 million. This factor was a significant predictor of successful outcomes. Other important factors included a recipient's age and weight, diagnosis, and cytomegalovirus-negative test results.

As a result of the issues raised above, some experts in the field of stem cell transplantation have noted that FDA should require premarket approval for cord and peripheral blood stem cell transplantation, whether or not the

³⁵Stem cells have varying degrees of "stemness"—that is, the range of more specialized cells that they can create. Some stem cells can replicate extensively but have only a limited capacity for differentiation. Thus, some stem cells can become only red blood cells while others may be able to form red or white blood cells or platelets. The most fundamental stem cell is the totipotent cell. In principle, one of these cells could reconstitute the entire blood producing and immune system. Pluripotent cells are less general but they can still differentiate into several "lines" that form different types of blood cells.

³⁶I. Webb and others, "Kinetics of Peripheral Blood Mononuclear Cell Mobilization with Chemotherapy and/or Granulocyte-Colony Stimulating Factor: Implications for Timing and Yield of Hematopoietic Progenitor Cell Collections," *Transfusion*, Vol. 36 (1996), pp. 160-67.

³⁷E. Gluckman and others, "Outcome of Cord-Blood Transplantation from Related and Unrelated Donors," *New England Journal of Medicine*, Vol. 337 (1997), pp. 373-81.

³⁸The HLA system includes a complex array of genes and their molecular products that are important in immune regulation, transplantation, and transfusion. It is second in importance to the ABO antigens in influencing the survival of transplanted solid organs, and immunologic recognition of differences in HLA antigens is probably the first step in the rejection of transplanted tissue.

cells were obtained from a close blood relative or a stranger, because such transplants are not yet well characterized. Other experts in stem cell transplantation from both academia and industry, including FACHT and the American Society for Clinical Oncology, have opposed such an approach. Private cord blood banks also disagree, stating that they would be put out of business by premarket approval requirements because federal statutes forbid profitmaking when a product has premarket approval status.

In sum, several safety issues arise when transplanting metabolic cells. Stem cells and other products characterized by a metabolic mode of action usually rely on viable, functioning cells. They are therefore sensitive to collection, processing, and storage perturbations and may not retain normal function after transplantation. Because transplantation therapy is routinely used to reconstitute the blood of patients whose own defective blood cells have been completely destroyed by chemotherapy or irradiation, the failure or improper functioning of such products could end in a broad variety of systemically adverse events, including death. We are concerned that the state of knowledge about these tissue therapies is not well characterized and poses equivalent risks to recipients whether the source of stem cells is a relative or an anonymous donor.

Some Processing Techniques May Affect Safety and Efficacy

The proposed approach considers the processing of cells and nonstructural tissues to be more than minimal manipulation when it alters the biological characteristics (and, thus, potentially the function or integrity) of the cells or tissues or when it is unknown whether it will alter them. Examples include cell expansion, activation, and genetic modification. More than minimally manipulated cells or tissues would be subject to processing controls and to premarket requirements to determine safety and effectiveness. FDA would evaluate the processing techniques in the course of reviewing premarket applications and would inspect firms to assess their operations and review their processing techniques before granting marketing approval.

The proposal is different for minimally manipulated tissues. For these tissues, FDA would require that the validation of the procedures be documented and available when FDA inspects a facility but would not require the submission of any information on processing. The proposed approach considers the processing of cells and tissues to be minimal manipulation when it does not alter their original relevant characteristics, such as those relating to the ability of cells or tissues to carry out the

function of reconstruction or repair. Examples include cutting, grinding, and shaping; soaking in antibiotic solution; sterilization by ethylene oxide or gamma irradiation; cell separation; and cryopreservation. Tissues that were processed with minimal manipulation would be subject to good tissue practices relating to contamination, integrity, and function that FDA would establish in future rulemaking. However, FDA currently has limited information on which to base criteria for these practices, and we found few processing techniques that had been validated by tissue facilities and evaluated by FDA for safety and effectiveness.

In several interviews, we obtained information regarding processes some facilities use that may be harmful to the efficacy of tissues or that have no established safety or efficacy record (for example, the use of bleach and peroxide or “air drying”). We did not independently verify what we were told. Below, we present information we gathered from these interviews and from the scientific research that highlights potential safety and efficacy issues. Some procedures that remove or destroy bacteria hamper the ability of tissue to remain viable. For instance, sterilization can destroy the viability of grafts, and irradiation and freeze-drying both reduce biomechanical strength. Therefore, cryopreserved skin, heart valve, and osteochondral bone grafts cannot be treated with these methods. Furthermore, chemical sterilization by exposure to ethylene oxide or demineralization techniques may adversely affect the regenerating properties of bone, although the evidence is controversial.³⁹ Similarly, although many tissue facilities use dimethyl sulfoxide in their cryopreservation practices, FDA has not approved this product for such purposes.

Ethylene oxide has been used with fluorocarbon (or freon) in an inactivation technique for tendons. However, it has been shown to result in residuals that were carcinogenic and deteriorated the tendons. Some tissue facilities use bleach and peroxide on bones, although this causes structural weaknesses. Also, other facilities have advertised the use of “air drying,” although this technique is unfamiliar to some tissue facility officials as an efficacious tool for inactivation. Gamma radiation is also used to process bone. For weight-bearing transplants, this process has been found to increase susceptibility to fracture (not all processors use this technique, but some do). Irradiation may be a good viral inactivation procedure, but it can cause mechanical problems in the processed bone.

³⁹E. Conrad and others, “Transmission of the Hepatitis-C Virus by Tissue Transplantation,” *Journal of Bone and Joint Surgery*, Vol. 77A (1995), pp. 214-24.

Although some physical and chemical agents have been shown to reduce the likelihood of isolating virus from treated solid tissues, we found no conclusive evidence that those processes render solid tissue completely safe and structurally intact.⁴⁰ In a case of HIV transmission through the use of fresh-frozen bone allografts from a donor who was negative on HIV screening but who infected four organ recipients and three of four recipients of fresh-frozen bone, it was found that more than 25 other recipients of tissue from this donor did not become infected.⁴¹ The latter group were transplanted with tissues that were relatively avascular; thus, it is unclear whether HIV transmission was absent because of processing or vascularity or both.

Although processes used to clean, sterilize, and render infectious agents harmless may affect the safety and efficacy of the tissue being processed, FDA officials agree that they have little information about the types of techniques currently in use and that they have not specified the processes that can be used safely and efficaciously. The proposed approach would require that facilities validate their procedures for safety and efficacy and make this information available to FDA upon inspection. However, the proposed approach would not require facilities to notify FDA of processing techniques defined as minimal manipulation, nor would facilities be required to submit safety and efficacy data on those processes. Submitting this information to FDA would provide the agency with a baseline understanding of industry practice.

Conclusions

In its proposed approach, FDA addresses three problems we identified as not covered in the current regulation: registration of tissue banks, oversight of reproductive and stem cell facilities, and false product claims. However, the proposed approach is still in its formative stages and will be codified over a number of years. Until then, these concerns will remain.

We identified two problems that are not addressed in either FDA's current regulation or its proposed approach. We found that some public umbilical cord blood banks obtain informed consent after collecting the blood. The safety implications of using units from mothers who may not have received prenatal care or who are called upon to answer questions postcollection about high-risk behavior are unknown. Requesting informed consent before delivery provides the mother with the

⁴⁰CDC, "Guidelines for Preventing Transmission of Human Immunodeficiency Virus."

⁴¹T. Eastlund, "Infectious Disease Transmission Through Cell, Tissue, and Organ Transplantation: Reducing the Risk Through Donor Selection," *Cell Transplantation*, Vol. 4 (1995), pp. 455-77.

information and opportunity to make a decision before a procedure is performed. Second, the lack of disclosure of genetic testing for donated reproductive tissues limits vital information that, if otherwise available, might alter a recipient's decision to use tissues from donors who could introduce genetic anomalies.

In four instances, we found that the proposed approach addresses issues that are not covered in the current regulation but does so in a manner that is inadequate to eliminate potential safety problems. First, the proposed approach would not require the reporting of any errors or accidents, even those that could have serious consequences. Without such reporting, FDA will miss an opportunity to provide warranted oversight. Second, FDA has an inadequate system for tracking tissues to recipients from donors who are later determined to have been virally infected or whose tissues should otherwise not have been transplanted. The inability to trace potentially infectious or otherwise hazardous tissues could have serious public health consequences. Third, FDA plans to require premarket approval for therapies using stem cells if the cells are obtained from an unrelated allogeneic donor. As a matter of policy, FDA will waive this requirement if the cells are obtained from oneself (autologous) or from a close blood relative (related allogeneic). However, the scientific community has not determined optimal collection, separation, processing, and storage procedures for these cellular-based tissues. Because these products are used to reconstitute a patient's entire immune system, the treatment poses great risk, regardless of whether the source is a relative or an anonymous donor. Fourth, we found that facilities have validated and FDA has evaluated few processing procedures. Some procedures currently in use may, in fact, harm the viability of grafts, reduce their biomechanical strength, and negatively affect the regenerating properties of bone. Without baseline knowledge of industry practice, FDA is hampered in its ability to fully monitor the safety of this aspect of human tissue banking.

We believe that steps that would generally incur minimal additional cost to the tissue-banking industry could be taken to address these concerns. Many of these steps, requiring little change in the majority of tissue-banking facilities, would correct practices that are not up to industry standards. Two areas could require that additional, more costly, steps be taken: the creation of a system for tracking tissues to recipients and the imposition of premarket controls upon related allogeneic stem cell therapies if FDA determines that adequate safety and efficacy data are not available after the moratorium it has proposed. However, we believe that actions should be taken if risks outweigh costs, as we believe is likely.

Recommendations

We recommend that the Secretary of the Department of Health and Human Services direct FDA to take action in several areas to improve the safety and efficacy of donated human tissue and to increase FDA's ability to regulate tissue facility activities.⁴² FDA should move ahead with its plan to require

- tissue facilities, including reproductive and stem cell facilities, to register with FDA;
- reproductive and stem cell facilities to adhere to all requirements of the current regulation;
- facilities that collect and store cord blood to provide accurate oral and written communication to consumers with regard to the state of knowledge of collection, processing, and storage techniques, as well as the likelihood of requiring cord blood transplantation, and to portray the risks and benefits relative to other therapies.

FDA should also add to its oversight plans provisions that would require

- tissue facilities to obtain informed consent before procuring any tissues intended for transplantation from living donors;
- disclosure of genetic tests that have been performed on donated reproductive tissues;
- tissue facilities to report serious error and accidents to FDA ("serious" to be defined in consultation with industry representatives);
- facilities that collect, store, process, distribute, or transplant human tissues to establish validated systems to track tissues to consignees and recipients;
- tissue facilities that collect, store, process, or distribute allogeneic peripheral stem cells or any cord blood stem cells to make premarket submissions if FDA determines that adequate safety and efficacy data are not available to license such products; and
- tissue facilities to inform FDA of the types of processing techniques used on tissues and to supply information on the safety and efficacy of these techniques.

Agency Comments and Our Response

In commenting on a draft of this report, FDA generally concurred with our recommendations to require (1) the registration of all tissue facilities with FDA, (2) adherence of reproductive and stem cell facilities to all the requirements in the current regulation, (3) accurate labeling and promotion by facilities that collect and store cord blood, (4) disclosure to

⁴²We define tissue facilities in these recommendations as covering both tissue and stem cell facilities.

recipients of genetic tests performed on reproductive tissues, and (5) validation of systems to track tissues to consignees and recipients.

The agency partly concurred with our recommendations on (1) reporting errors and accidents to FDA, (2) requirements for premarket submissions by peripheral and cord blood stem cell facilities, and (3) tissue facilities' informing FDA of the types of processing techniques they use and the safety and efficacy data of these techniques.

FDA agreed that adverse events should be reported to the agency but pointed out that reviewing error and accident reports would cost resources for both FDA and the industry and that current budgeting constraints would not allow FDA to review and evaluate such reports. We understand the fiscal ramifications of requiring error and accident reporting, and it is for this reason that we recommended that only "serious" errors and accidents be reported to FDA.

FDA noted that it intends to require premarket applications for unrelated allogeneic cord blood stem cells but would not require such submissions for family-related allogeneic transplants because FDA was trying to accommodate the needs and concerns of families. However, we are unaware of safety issues that would be relevant only for unrelated allogeneic cord blood transplants. For this reason, we recommended that facilities that collect, store, process, or distribute peripheral or cord blood stem cells make premarket submissions if FDA determines that adequate safety and efficacy data are not available to license such products.

FDA also pointed out that while it intends to review the processes tissue facilities use before approving highly manipulated tissue products, it will require validation to be documented and available during FDA inspections for procedures involving only "minimal" tissue manipulation. However, we are concerned about the time that could elapse before the agency learns about the safety and efficacy of these processes. Because FDA does not plan to conduct routine inspections of tissue facilities, the agency may not have the opportunity for many years to evaluate the documentation.

FDA did not concur with our recommendation that informed consent be obtained from living donors before procuring tissues intended for transplantation. The agency believes that seeking informed consent for the use of cord blood after collection does not raise any additional safety concerns, but it states that current investigational protocols will provide the opportunity to assess this. We point out that obtaining informed

consent before infant delivery affords mothers sufficient time to deliberate decisions before procedures are performed.

FDA's comments and our response are provided in greater detail in appendix II. The agency provided a number of technical comments that we have not reprinted but did incorporate into the report as appropriate.

As we arranged with your office, unless you publicly announce the report's contents earlier, we plan no further distribution until 15 days after it is issued. We will then send copies to the Secretary of the Department of Health and Human Services, the Commissioner of FDA, and others who are interested. We will also make copies available to others upon request.

If you have any questions or would like additional information, please call me at (202) 512-7119 or Marcia Crosse, Assistant Director, at (202) 512-3407. Major contributors to this report are listed in appendix III.

Sincerely yours,

A handwritten signature in cursive script, reading "Bernice Steinhardt".

Bernice Steinhardt
Director, Health Services Quality
and Public Health Issues

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Abbreviations

AABB	American Association of Blood Banks
ASBMT	American Society for Blood and Marrow Transplantation
AATB	American Association of Tissue Banks
ASRM	American Society for Reproductive Medicine
CDC	Centers for Disease Control and Prevention
EBAA	Eye Bank Association of America
FAHCT	Foundation for the Accreditation of Hematopoietic Cell Therapy
FDA	Food and Drug Administration
GVHD	graft versus host disease
HCFA	Health Care Financing Administration
HHS	Department of Health and Human Services
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRSA	Health Resources and Services Administration
HTLV	human T-cell lymphotropic virus
IND	investigational new drug
ISHAGE	International Society of Hematotherapy and Graft Engineering
NHLBI	National Heart, Lung, and Blood Institute
NMDP	National Marrow Donor Program
OPO	organ procurement organization
PHS	Public Health Service

Additional Information on Tissue-Banking Processes

Procurement

Ideally, each potential tissue or organ donor encounters only one organization capable of performing all aspects of the donation process, but this rarely occurs. Indeed, donors of multiple tissues or organs may encounter as many as 10 different transplant-related programs. Tissue donors who also donate organs are coordinated by the federally designated organ procurement organization (OPO) in the area.⁴³ Organs are almost always recovered from heart-beating donors, but they may also be collected from nonheart-beating donors. In the case of organ donation, the OPO is usually the main point of contact for the many steps between contacting the family of a potential donor and tissue or organ recovery. While the screening requirements and procedures of OPOs and tissue banks are basically the same, they do sometimes differ. Moreover, while OPOs are generally required by law to establish agreements with tissue facilities operating within the same service area, the coordination between an OPO and its associated tissue facility is determined without definitive method by individual facilities.

Tissue brokers may procure tissue and distribute it but do not track it after they have sent it to other tissue banks or organ procurement organizations. Even these brokers will be considered tissue facilities under FDA's proposed approach. Tissue processors obtain tissue from different sources (OPOs, medical examiners, and tissue facilities) and are charged with processing the tissue. Some processors procure and process their own tissue as well as process tissue for other facilities; others work through contractual agreements with OPOs, medical examiners, and tissue facilities.

Tissues that are procured from donors include musculoskeletal tissues (bones, tendons, and cartilage), corneas, skin, reproductive tissues, and stem cells. Tissues are recovered from two types of donors and the procedures for accepting these donors vary slightly. Living persons can donate reproductive tissue in the form of sperm or eggs, stem cells from circulating blood or placenta or umbilical cord blood, eye tissue, and surgical bone recovered incidentally to a medical procedure. Bone, connective tissue, eye tissue, skin, and heart valves can be taken from cadavers.

Private cord blood banks collect and store cord blood for use in the event of disease in the infant or family members. These facilities have emerged

⁴³OPOs are responsible for recovering organs from donors. The National Organ Transplant Act requires that OPOs also arrange to cooperate with tissue facilities for the retrieval, processing, preservation, storage, and distribution of tissues as may be appropriate to ensure that all usable tissues are obtained from potential donors.

in recent years in response to some scientific evidence suggesting the benefits of cord blood transplantation over traditional bone marrow transplantation. Consumers pay about \$300 to \$1,700 for the collection, processing, and testing of the unit and an annual storage fee of about \$100. Public cord blood facilities also collect and store umbilical cord blood stem cells for allogeneic use in unrelated recipients. While there are no storage fees at these facilities, they charge transplant centers a fee (approximately \$15,000) for obtaining, processing, and storing the cord blood.

While policies and procedures vary by institution, the American Association of Tissue Banks (AATB) has clear standards for the acquisition of tissues. If a prospective cadaveric donor meets basic acceptance requirements for time and cause of death, the family is approached for consent. Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT) standards require informed consent from maternal donors of umbilical cord blood before or within 7 days of the delivery of the child.

Screening

Screening questions focus mainly on risk behaviors for infectious disease, genetic abnormalities, and degenerative neurological disease. The importance of following all screening steps is underscored by research at one tissue facility that found that 9.8 percent of 1,000 donors whose families provided a medical history negative for risk factors were rejected on disease testing or autopsy.⁴⁴ Table I.1 outlines the suitability criteria established by AATB.

Table I.1: Donor Suitability Criteria

Donor suitability criterion	Action
Excised, healed localized skin cancer, carcinoma-in-situ of the uterine cervix, or proven nonmetastatic primary brain tumor	Accept donor
History of other malignancies treated by surgery alone with no evidence of recurrence or spread for at least 5 years	Base decision on medical director's evaluation
History of autoimmune disease	Base decision on medical director's evaluation
Ingestion or exposure to toxic substances	Base decision on medical director's evaluation
Significant active infection (septicemia, systemic viral disease, untreated syphilis, active tuberculosis, systemic mycosis)	Reject donor

(continued)

⁴⁴Information provided by B. Buck at FDA workshop on human tissue intended for transplantation, Bethesda, Maryland, June 1994.

Appendix I
Additional Information on Tissue-Banking
Processes

Donor suitability criterion	Action
History of receiving pituitary-derived human growth hormone	Reject donor
History of dementia or degenerative neurological disorders of viral or unknown etiology	Reject donor
HIV or hepatitis risk factor	Reject donor
Current malignancy (except as noted above)	Reject donor
Rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, sarcoidosis, myasthenia gravis, metabolic bone disease	Reject as musculoskeletal tissue donor
History of leprosy (Hansen's disease)	Reject as skin donor
Family history of genetic disorders that may affect recipient	Reject as umbilical cord blood donor
Positive genetic tests for cystic fibrosis, sickle cell trait, Tay-Sachs disease, or thalassemia ^a	Reject as semen donor
Positive tests for Neisseria gonorrhea and Chlamydia trachomatis ^b	Reject as semen donor
Inadequate sperm quality and quantity ^b	Reject as semen donor
Age criteria established by facilities' standard operating procedures except as noted below — Older than 40 — Older than 60	Reject as semen donor Reject as cardiovascular tissue donor
History of bacterial endocarditis, rheumatic fever, or semilunar valvular disease	Reject as cardiovascular tissue donor

^aCystic fibrosis is the most common recessive disease in the Caucasian population and usually results in severe lung disease and other problems leading to early death. Sickle cell is found mostly in individuals of African ancestry. It results in a number of medical problems such as pain, increased risk of infection, and stroke. Tay-Sachs is a recessive disorder in which the activity of an important enzyme is deficient. The results are neurological complications and death before age 5. Thalassemia is found primarily in Asian, African, Middle Eastern, and Mediterranean groups. It results in a variety of medical problems and a need for lifelong blood transfusions and other complications.

^bNot performed for musculoskeletal, skin, eye, or stem cell donors.

In addition to these AATB criteria, standards the Eye Bank Association of America (EBAA) has established for eye donors include the rejection of donors with an unknown cause of death, active encephalitis, progressive encephalopathies, congenital rubella, Reyes syndrome, rabies, and intrinsic eye disease or certain prior eye surgeries. A physical examination checks for signs of intravenous drug use, recent tattoos or body piercing, swollen glands, and other indications of possible infection. The tissue facility's medical examiner reviews autopsy findings.

Testing

Donors who have received blood or fluid transfusions may have blood that is too diluted to detect infection, and a pretransfusion or infusion sample is then sought. If none is available, the donor's medical records should be examined to determine the acceptability of postransfusion or postinfusion blood specimens. Each tissue facility is also to develop a procedure for determining whether a postransfusion or postinfusion specimen can be used. This plasma dilution algorithm is to be used to determine if the amount of blood loss and fluid replacement is below the threshold that renders a postransfusion or postinfusion blood sample invalid for accurate testing of the donor's own blood for infectious diseases. If the results are above the threshold and no pretransfusion or preinfusion sample exists, the donor is rejected.

After death, cells in the blood system burst, creating a state known as hemolysis. Hemolyzed blood samples can lead to false positive test results, which is why test kit manufacturers caution against using such samples. False positive tests result in the destruction of donated tissue that is probably not infected and is, therefore, safe for use; they also cause undue concern among relatives who are notified of the donor's test results. Confirmatory tests often indicate noninfectivity, but these results cannot be used to invalidate possible false positives on initial tests. FDA is currently working with viral test kit manufacturers to validate these kits for use on cadaveric samples. However, because the number of donors is so few, the economic motivation for manufacturers to do so is low. Current regulations require that currently licensed test kits are to be used until FDA has given its approval and labeling of the test kits has been modified to specifically indicate their use for cadaveric blood specimens.

Processing

Processing musculoskeletal tissue varies but tends to follow certain procedures to ensure its safety. Processing occurs in clean, aseptic rooms. Single-donor processing uses air filtration and the tissue is cleaned with high-pressure lavage and ultrasonic techniques. It is also soaked in antibiotic and ethanol solutions and irradiated at low doses. It is then cut and shaped to certain specifications and is preserved by freezing or freeze-drying. Grafts are also cultured for microbiological testing. Tendons and ligaments do not go through an alcohol-processing step as bone does (alcohol is used as a defatter).

Skin is either cryopreserved or processed nonfrozen. Cryopreservation often begins within 72 hours of procurement, although AATB standards allow 96 hours. Skin is placed in a preservation solution that is then

replaced with 10-percent to 15-percent glycerol and allowed to incubate 20 to 60 minutes before freezing. Standards from AATB state that final cultures should be performed for specific organisms (for example, *serratia*, yeast or fungi, or *proteus*). AABB standards note that refrigerated skin is to be stored no longer than 14 days.

Corneas are excised and placed in a culture medium that is an FDA-approved medical device (there is only one manufacturer of this medium). A cornea can stay in the medium for up to 1 week but the usual time is 3 days. Corneas can also be cryopreserved, although this is rarely done. They are stored in liquid nitrogen with a cryoprotective agent, such as dimethyl sulfoxide, to prevent the formation of damaging intracellular ice crystals.

Donated semen can be used for both intrauterine and intracervical insemination. Processing donated semen for intrauterine insemination involves washing the ejaculate specimen to remove the seminal plasma contents before freezing. Specimens are then resuspended and frozen with a buffer (such as egg yolk citrate). Motility and total motile cells/ml are the same for both types of insemination. Semen that is shipped is usually kept in liquid nitrogen containers that keep the semen frozen for 7 to 10 days.

Cord blood is preserved in the short term in a liquid state in FDA-approved CPD anticoagulant for 24 hours at 1 to 6 degrees Celsius. It can also be stored after being cryopreserved in liquid nitrogen with dimethyl sulfoxide for 3 to 5 years at -85, -135, or -185 degrees Celsius. The frozen cells are thawed in a water bath, a dextran-albumin mixture is added, and the cells are then centrifuged. The supernatant, which contains the dimethyl sulfoxide, is then removed, and the cells are resuspended in more dextran and albumin and are transfused. This results in an increase in viable cells and an increase in colony-forming unit recovery over time. It also allows for the manipulation of the cells after thawing.

Comments From the Food and Drug Administration

Note: GAO comments supplementing those in the report text appear at the end of this appendix.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

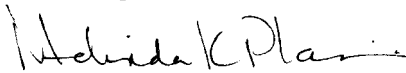
OCT 23 1997

Ms. Bernice Steinhardt
Director, HEHS
U.S. General Accounting Office
Room 5A26
441 G Street, N.W.
Washington, D.C. 20548

Dear Ms. Steinhardt:

Enclosed are the Food and Drug Administration's comments on the GAO Draft Report entitled "Human Tissue Banks: FDA Taking Steps to Improve Safety, But Some Concerns Remain," GAO/HEHS-98-25, November 14, 1997.

Sincerely,

for 
Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosure

**FOOD AND DRUG ADMINISTRATION COMMENTS ON THE GAO DRAFT REPORT
ENTITLED HUMAN TISSUE BANKS: FDA TAKING STEPS TO IMPROVE SAFETY, BUT
SOME CONCERNS REMAIN GAO/HEHS-98-25**

GENERAL

We appreciate the opportunity to review the draft report. It reflects well on the hard work the evaluation team put into understanding the very sensitive issues surrounding tissue transplantation. In general we find the report to be correct and, with the exceptions discussed below, we agree with the findings and recommendations. As we have previously stated, the Food and Drug Administration's (FDA or Agency) proposed approach to regulation of human tissue banking is a broad outline of the program we believe to be necessary to protect the public. The details will be provided in future specific regulations promulgated through notice and comment rulemaking.

GAO RECOMMENDATION

1. FDA should move ahead with its plan to require
 - tissue facilities, including reproductive and stem cell facilities, to register with FDA;
 - reproductive and stem cell facilities to adhere to all requirements of the current regulation;
 - facilities that collect and store cord blood to provide accurate oral and written communication to consumers with regard to the state of knowledge of collection, processing, and storage techniques, as well as the likelihood of requiring cord blood transplantation, and to portray the risks and benefits relative to other therapies.

FDA COMMENT

FDA concurs. While FDA plans to require that labeling and promotion for these tissue products be truthful, balanced, accurate, and non-misleading, the Agency does not plan to delineate the specifics of the information that must be provided to consumers.

GAO RECOMMENDATION

2. FDA should also add to its oversight plans provisions that would require
 - a. - tissue facilities to obtain informed consent before procuring any tissues for transplantation from living donors;

See comment 1.

FDA COMMENT

FDA does not agree with this recommendation at this time. GAO is concerned that a new mother (just post delivery) might not answer truthfully high risk questions that could result in removing her newborn from her care. FDA is mindful of the need to obtain informed consent from the mother without undue coercion, regardless of whether this occurs before or after collection. The Agency is not aware of any studies that would indicate that the untruthful response would be more likely post delivery than predelivery. FDA believes that seeking informed consent for use of the cord blood after collecting umbilical cord blood does not raise any additional safety concerns than would be raised by seeking informed consent before collecting cord blood. It is equally possible to decline without justification if informed consent is sought after collection. The current cord blood banking protocols, operating under FDA-accepted Investigational New Drugs (IND), will, however, provide the opportunity through data collection to assess the safety and risks of obtaining informed consent after cord blood has been collected. If we learn that the timing of informed consent affects the safety of the tissue, we will modify our position.

GAO RECOMMENDATION

- b. - disclosure of genetic tests that have been performed on donated reproductive tissues;

FDA COMMENT

In general, FDA agrees that recipients of tissue should know, through appropriate labeling of the tissue, the results of testing performed. Ethical, scientific, and regulatory issues regarding genetic tests are currently under discussion within the Department of Health and Human Services in connection with the final report of the Task Force on Genetic Testing, Promoting Safe and effective Genetic Testing in the United States, Holzman, N. A. And Watson, M. S. Eds. (Sept. 1997). The GAO's recommendation will be considered as part of that broader effort.

GAO RECOMMENDATION

- c. - tissue facilities to report serious errors and accidents and adverse events to FDA ("serious" to be defined in consultation with industry representatives);

FDA COMMENT

FDA concurs in part. With respect to adverse events, FDA plans to promulgate through notice and comment rulemaking regulations to require adverse event reporting. With respect to errors and accidents reporting, FDA agrees that more information might allow the Agency to make a better assessment of overall compliance by the tissue industry. The recommended requirement, however, would be resource intensive for the Agency and for the industry. Current budgeting constraints would not allow FDA to review and evaluate such reports. Facilities are required to

See comment 2.

maintain records of errors and accidents, however, and to make such records available for FDA review during inspections. Further, the cellular and tissue products FDA is proposing to regulate under section 361 of the Public Health Service Act (PHSA) are the lower risk products that present a lesser public health concern. Products that will be regulated under section 351 of the PHSA and/or under the Federal Food, Drug and Cosmetic Act (FFDCA) will be subject to reporting requirements commensurate with other biologics, drug, and medical device reporting.

GAO RECOMMENDATION

- d. - facilities that collect, store, process, distribute, or transplant human tissues to establish validated systems to track tissues to consignees and recipients;

FDA COMMENT

We concur. FDA intends to require that manufacturers of cellular and tissue-based products have systems in place that will allow tracking of tissue products from the donor to the recipient. The proposed approach mentions good tissue practices, but does not elaborate on the specific practices that would be required. Table 1 of the proposed approach mentions product tracking. Tracking also was discussed by FDA at a public meeting on March 17, 1997. The specifics of any tracking system will be developed through notice and comment rulemaking.

GAO RECOMMENDATION

- e. - tissue facilities that collect, store, process, or distribute allogeneic peripheral stem cells and any cord blood stem cells to make premarket submissions if FDA determines that adequate safety and efficacy data are not available to license such products; and,

FDA COMMENT

FDA agrees in part with this recommendation. FDA intends to require IND applications for unrelated allogeneic cord blood stem cells if the Agency determines that adequate safety and effectiveness data are not available to license such products. By distinguishing family-related allogeneic from unrelated allogeneic donors of umbilical cord blood stem cells, however, FDA is making an effort to accommodate the concerns and needs of families. FDA expects that standards developed for unrelated allogeneic cord blood will be applied to family-related allogeneic cord blood collection through good tissue practices.

GAO RECOMMENDATION

- f. - tissue facilities to inform FDA of the types of processing techniques used on tissues and supply information on the safety and efficacy of these techniques.

See comment 4.

FDA COMMENT

FDA concurs in part with this recommendation. With respect to those tissue products that pose higher risks, (e.g., more than minimally manipulated, not homologous, etc.) FDA intends to require premarket review, which includes evaluation of the processes used in manufacturing the product. FDA's limited resources, however, have made it necessary to prioritize review of products to those with the greatest risk. In its proposed approach, FDA has made a distinction between procedures that minimally manipulate the tissue and other procedures that manipulate the tissue to a greater degree. In general, the minimally manipulated procedures have been in use for quite some time and have become generally standardized. For these minimal procedures, FDA will require that validation of the procedure be documented and available when FDA inspects the facility. FDA will use the inspection as an opportunity to gather information on these processes also. See Attachment A for further details of FDA's inspection guidance for tissue banking.

Procedures that manipulate the tissue more than minimally (usually novel procedures that have not been generally accepted or standardized by the industry) will require review and approval by FDA when a premarket application is submitted for the product.

In addition to the above comments, we have several technical corrections listed below. Again, we appreciate the efforts that went into evaluating the tissue banking issues and producing this report.

The following are GAO's comments on FDA's October 23, 1997, letter.

GAO Comments

1. We believe that the current umbilical cord blood banking protocols, operating under FDA-accepted INDs, will be worthwhile in ascertaining the safety consequences of obtaining informed consent for cord blood collection after delivery. This information should be used to determine the manner and time at which collection is to take place. However, it should be noted that a working group on ethical issues in cord blood banking concluded that informed consent should be obtained before procuring placental blood for transplantation because not obtaining consent before delivery does not allow mothers to make decisions before collection.⁴⁵ Additionally, obtaining consent before birth accords mothers sufficient time to deliberate any decisions they might have made before the collection began.
2. We believe that FDA's requirement that facilities maintain records of error and accidents and make them available for FDA review during inspections is worthwhile. However, we believe that serious errors and accidents, such as the distribution of unacceptable tissues, should be reported to FDA so that the agency may take immediate action if such problems threaten the public health. Presently, FDA might not learn of such incidents until after it has performed an inspection. FDA officials have noted that they do not plan to conduct routine inspections of tissue facilities. Furthermore, FDA's present authority to seize tissue products and enjoin tissue facilities is available only for products that are more than minimally manipulated, nonhomologous, and so on. By requiring tissue facilities to report serious errors and accidents, FDA would be able to obtain information pertinent to activities that might compromise human tissue safety or effectiveness.
3. We understand that FDA intends to allow the cord blood stem cell community time to collect information that would provide the agency with adequate data to promulgate standards. FDA officials have stated that if they cannot determine that adequate safety and effectiveness data are available, unrelated allogeneic cord blood stem cell transplants would require an IND. These officials have also noted that an IND would not be required for family-related allogeneic stem cell transplants because FDA is trying to accommodate the concerns and needs of families. However, as we point out in our report, different collection and processing techniques

⁴⁵The Working Group on Ethical Issues in Umbilical Cord Blood Banking was supported by the Cannon Foundation, Concord, North Carolina, and the Kenan Program in Ethics at Duke University, Durham, North Carolina.

can affect levels of bacterial contamination and the viability of the stem cells, and collection, processing, and storing methods are not yet well characterized within the cord and peripheral blood stem cell communities. The mitigation of these problems is not related to where one obtains these stem cells (autologous, family-related, or unrelated allogeneic). As a result, there is no scientific basis on which to make a demarcation for premarket submissions based on the source of the stem cell, and we believe that patients whose source of stem cells is a family member should be afforded the same safety considerations as those who obtain stem cells from someone unrelated.

4. We agree with FDA's position that certain products should require premarket review (for example, more than minimally manipulated or not homologous) that would also include an evaluation of their manufacturing processes. We also agree with FDA's position that tissue facilities should be required to validate processing procedures for products that do not fall under such categories and have documentation available for FDA inspection. However, we have provided information in our report on processing techniques that may result in only minimal manipulation but may destroy the viability of grafts, affect biomechanical strength, and hamper the regenerating properties of bone. Thus, we are concerned about these processes still being employed before the codification of a requirement to maintain validation studies. Additionally, since FDA does not intend to conduct routine inspections of tissue facilities, the agency will not have adequate opportunity to evaluate the documentation of these validation studies. Once facilities are required to document the validation of their procedures, it would pose little burden to ask that the documentation be submitted to FDA rather than waiting for inspections. For these reasons, we believe that information on these processing techniques should be provided to FDA so that the agency can ascertain their safety and efficacy in a timely manner.

Major Contributors to This Report

Marcia Crosse, Assistant Director
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